REMARKS

Applicants note that the amendments hereinabove are presented in the Revised Format of Amendments as described in the Flyer from the USPTO dated 2/13/03.

Claims 1-19 are pending in the instant application. The Examiner has required a restriction and has made it final. The Examiner has also rejected the claims now under consideration (Claims1-13 and 18) for various reasons set out below. In light of the Restriction Requirement and in response to the rejections, Applicant have amended Claims 1, 4 and 10-12, cancelled Claims 3, 14-17 and 19 (without prejudice to filing a divisional application directed thereto) and added new Claim 26. Applicant respectfully requests reconsideration of the application in light of the amendments and the following remarks.

The Examiner has rejected Claims 1-2, 11 and 18 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner suggests that the genus "cytotoxic agent-oligopeptide conjugate" does not meet the written description requirement because the term cytotoxic agent is not a precise definition, but is instead defining the compounds by a functional activity. Applicant respectfully contends that the definition of cytotoxic agent is well known to a person of ordinary skill in the art. However, in order to advance the prosecution of this application, Applicant has amended Claim 1 to be directed to conjugates of vinca alkaloids and oligopeptides. Applicant notes that because such a limitation was found in Claim 3 of the application as originally filed, this amendment does not introduce and new matter. Applicant expressly reserves that right to pursue the invention wherein the cytotoxic agent is selected from other known agents.

In light of the amendment to Claim 1, Applicant respectfully contends that the Examiner's rejection under 35 U.S.C. §112, first paragraph is now moot and should be withdrawn.

The Examiner has rejected Claims 9-13 and 18 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and claim the invention. The Examiner first points out that in Claim 9 two different compounds have the same sequence. Applicant respectfully contends that the Sequence Listing that was prepared focused on the amino acid

sequence and N-terminus protecting group of the oligopeptide component of the conjugate. In formulating the Sequence Listing, Applicant did not include in the amino acid "feature" description the C-terminus vinca alkaloid component and/or a linker unit with a unique structure. Applicant attempted to be consistent with this approach throughout the Sequence Listing. Therefore, in Claim 9, the fifth and sixth compounds listed were considered to be described by the same Sequence Listing number. While Applicant respectfully contends the choice of which parts of a molecule to include as a "feature" may be made at Applicant's discretion, Applicant would be willing to amend the sequence numbers and the Sequence Listing if the application is considered to be in condition for allowance except for that designation.

The Examiner suggests that Claim 10 is indefinite because it is not clear what is "selected from". Applicant has amended Claim 10 and added new Claim 26 so that the compounds wherein "peptide" is varied appear in Claim 10 and the two individual "entire formula" compounds appear in Claim 26. In light of this amended, Applicant respectfully contends that the claiming of those species has been clarified and is no longer indefinite.

The Examiner suggests that Claims 11, 12 and 18 are indefinite because they refer to "a compound of Claim 1" while the subject matter of Claim 1 is a "conjugate". Applicant has amended Claims 11, 12 and 18 to refer to the "conjugate of Claim 1". In light of these amendments, Applicant contends that those claims are no longer indefinite.

In light of theremarks above, the amendments to Claims 1, 4, 10-12 and 18 and the deletion of Claim 3, Applicants respectfully contend that the Examiner's rejection of Claims 9-13 and 18 under 35 U.S.C. §112, second paragraph, is moot and should be withdrawn.

The Examiner has rejected Claims 1-6, 11-12 and 18 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 3-5 and 11-12 of U.S. Pat. No. 5,866,679 ('679 patent) and the teaching of Metzler in *Biochemistry*. The Examiner notes that the '679 patent teaches a conjugate comprising an oligopeptide and a cytotoxic agent with specific formulae in the patent showing an X_L linker which is either absent, an amino acid or a diaminoalkyl. The Examiner notes that the '679 patent does not disclose a linker having a oxygen "end" or forming an ester linkage. The Examiner however suggests that the

Biochemistry text teaches that under physiological conditions amides and esters undergo displacement reactions wherein the carbonyl moiety-oxygen/nitrogen bond is cleaved.

Applicant respectfully contends that combined disclosure of those two references at best suggests that it might obvious to try other potential linkers between the cytotoxic agent and the cleavable oligopeptide. The mere suggestion that additional linkers might be obvious to try is not sufficient under the statute to make such an invention obvious.

In fact the disclosure of the *Biochemistry* reference might instead teach away from trying the modification of the previously disclosed diamine linker to the aminoalkyl hydroxyl linker, since the design of the conjugate of the instant invention preferably includes stability to endogenous non-PSA serum enzymes. Thus, Applicant contends that the disclosure of the '679 patent in light of the *Biochemistry* text does not render the instantly claimed linker obvious and the Examiner's rejection of Claims 1-6, 11-12 and 18 under the judicially created doctrine of obviousness-type double patenting is untenable and should be withdrawn.

The Examiner has rejected Claims 1-6, 11-12 and 18 under 35 U.S.C. §102(e) as being anticipated by the '679 patent noted above. The Examiner suggests that the broad generic claims (Claims 11-13) of the '679 patent teach the instantly claimed conjugates. Applicant respectfully notes that the claims cited by the Examiner are directed broadly to the conjugates comprising a cytotoxic agent and a cleavable peptide, optionally connected via a chemical linker. Applicant notes that those claims encompass the compounds of the instant invention, but the '679 claims do not disclose all of the elements of the instant claims. In particular, the '679 patent claims do not disclose the required presence of a hydroxyalkyl amino chemical linker between the vinca alkaloid cytotoxic agent and the cleavable peptide, as is instantly claimed.

It is a well established principle of patent law that a broad generic teaching in the prior art does not anticipate a later invented species or sub-generic formula. Because the hydroxyalkyl amino chemical linker is not specifically disclosed in the '679 patent claims or specification, the Examiner's rejection of Claims 1-6, 11-12 and 18 under 35 U.S.C. §102(e) as being anticipated by the '679 patent is untenable and should be withdrawn.

The Examiner has rejected Claims 1, 3-4, 7 and 18 under 35 U.S.C. §102(e) as being anticipated by the disclosure of U.S. Pat. No. 5,948,750. The Examiner suggests that all of the elements of the instantly claimed vinca drug-oligopeptide conjugate are disclosed in the '750 patent. In particular the Examiner suggests that the hindered hydroxyalkyl amino linker (which is incorporated into the instantly claimed compounds) is disclosed in '750 patent.

Applicant respectfully notes however that the element of the instantly claimed conjugate that makes it distinct from the disclosure of the '750 patent (the incorporation of a sterically hindered substituted hydroxyalkylamine linker) is not disclosed in the '750 patent. Applicant notes that the '750 patent merely discloses an unsubstituted diamino alkyl linker (see col. 23, line 42 and col. 27, line 41 to col. 28, line 6). Applicant notes that while the '750 patent suggests that other linkers are contemplated, it does not specifically disclose any other potential linkers and gives no guidance as to what those other linkers might be. Because the instantly claimed conjugates incorporate a hydroxyalkylamine linker and that type of linker is not disclosed in the '750 patent, Applicant contends that the rejection under 35 U.S.C. §102(e) is untenable and should be withdrawn.

Furthermore Applicant contends that nor the '750 patent does not render the instantly claimed compounds obvious. Applicant notes that there is no teaching in the '750 patent of any specific linkers with respect to a vinca alkaloid conjugate other than an alkyldiamine linker (as noted above). Applicant contends that there is no teaching or suggestion in the '750 patent that one would selectively choose a hydroxyalkylamine as such a linker and that one of ordinary skill in the art would furthermore modify such a simple straight chain linker analogous to the type disclosed in the '750 patent by incorporating sterically bulky substituents on the linker. Applicant therefore respectfully contends that the disclosure of the '750 patent does not teach or suggest the instantly claimed conjugates and provides no motivation to one of ordinary skill in the art to modify any conjugate disclosed therein to arrive at the instantly claimed compounds. As such, Applicant respectfully contends that the pending instant claims are also unobvious in light of the '750 patent.

Applicant respectfully contends that the Examiner's rejection of Claims1-13 and 18 is now untenable and moot, and that Claims 1, 2, 4-13 and 18 as amended and new claim 26 are allowable and an early Notice of Allowance is earnestly solicited. If a telephonic communication

with Applicant's representative will aid in the advancement of the prosecution of this application, please telephone the representative indicated below.

Respectfully submitted,

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Date: October 9, 2003